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Observations of the Site-Specific Carcinogenicity of Vinyl Chloride to Humans

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A review of epidemiologic studies of workers exposed to vinyl chloride (VC) was conducted. Some of these studies comprised small cohorts and thus were insensitive in the evaluation of carcinogenic response for sites that do not demonstrate a high relative risk. Other larger studies used methodology and design that precluded an interpretation of the results. Such limitations were acknowledged by some authors.

Use of restrictive disease rubrics also lead to the submerging of sites that would have demonstrated significant excesses. For example, some investigators analyzed data for liver cancer deaths with the board category of digestive system cancer deaths, while others combined data for CNS cancer deaths with the broad cateogry of "other and unspecified cancer," and most studies analyzed information for lymphatic and hematopoietic system cancer deaths with all data combined. Only four of eight studies reviewed could demonstrate a significant excess of liver cancer among VC-exposed workers—a site confirmed in humans by 1974. In contrast, five of eight studies appear to demonstrate a significant excess of CNS cancer mortality. Workers exposed to VC also demonstrate a significant excess of mortality for lung cancer, while the data for lymphatic and hematopoietic system cancer are suggestive. Interpretation of cancer of the latter systems may have been clarified if investigators had not analyzed their data by broad disease classifications.

In 1930, shortly after vinyl chloride (VC) was introduced into commerce, VC toxicity was reported in experimental animals (*1*). Over the next five decades, study throughout the world indicated that employment in the VC industry was associated with a wide range of toxicity in humans. This toxicity has included nonmalignant pathologic effects or symptoms, involving (but not limited to) the bones, liver, central nervous system (CNS), lungs, and blood (*2*).

Between 1970 and 1974, experimental bioassay demonstrated VC-induced cancer in multiple organs including the liver, brain, lungs and lymphatic system (*3*, *4*). This carcinogenic response has been observed in several species, given a wide range of doses, by various routes of administration.

Between 1973 and 1977, several epidemiologic studies were undertaken to assess the site-specific cancer risk among workers exposed to VC. For this presentation, findings of these studies will be limited to an assessment of cancer of four organs or organ systems in humans. These same sites are known to be associated with nonmalignant VC-related disease or symptoms in humans and cancer in experimental animals.

Liver Cancer in Humans

Table 1 shows a summation of data from the epidemiologic studies as related to liver cancer. Some authors did not present site-specific analyses for liver cancer deaths. Therefore, the most specific information available is presented.

Waxweiler et al. (*5*) conducted a cohort study of workers who had been exposed to VC in the U.S.

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Table 1. Epidemiologic study results of VC-exposed workers as related to biliary and liver or digestive system cancer deaths.

Investigation	Site	Deaths		
		Observed	Expected	SMR
Waxweiler et al. (*5*)	Biliary and liver			
Total cohort		7	0.6	1155[a]
Latency > 15 yr		7	0.4	1606[a]
Byren et al. (*6*)	Liver and pancreas			
Total cohort		4	0.97	413[b]
Latency > 10 yr		4	0.68	589[a]
Fox and Collier (*7*)	Liver			
Total cohort		4	1.64	244
Plant #2 > 15 yr		3	0.13	2308[a]
Seven other plants		1	1.51	66
Monson et al. (*8*)	Biliary and liver			
Total deaths		8	0.7	11.0[b,c]
Tabershaw and Gaffey (*9*)	Digestive organs			
Total cohort		19	21.7	94
Highest exposure, > 5 yr employment		11	7.5	151
Buffler et al. (*10*)[d]				
Ott et al. (*11*)[e]				
EEH (*12*)	Digestive organs			
Total cohort		29	40.8	71
Latency > 20 yr		9	13.6	70

[a] $p < 0.01$.
[b] $p < 0.05$.
[c] Proportional mortality study risk ratio.
[d] No liver cancer identified among 8 cancer deaths.
[e] No liver cancer identified among 20 cancer deaths.

for at least five years and who had achieved a period of ten or more years since initial exposure (latency). On the basis of seven liver and biliary cancer deaths that fit the cohort definition, the study demonstrated an 11-fold to 16-fold excessive risk of death from cancer of this site among VC-exposed workers. These findings represent an underestimate of the risk because seven additional individuals who died from liver/biliary cancer at the plants being studied were not included in the analyses. Of these latter seven cases, four individuals diagnosed with liver angiosarcoma were still alive at the study cut-off date, while two individuals who died from biliary cancer had incomplete information on length of exposure to VC. A seventh individual did not fit the study cohort definition as he was exposed for only three years. He died from liver angiosarcoma 17 years after his initial exposure to VC.

Byren et al. (*6*) conducted a cohort study of all Swedish workers ever employed in positions where exposure to VC could have occurred. The investigators combined deaths from cancer of the liver and pancreas because they believed that there was some overlap in reporting. There were four liver/pancreatic cancer deaths observed, compared to 0.77 expected ($p < 0.02$). An additional death from liver angiosarcoma was identified as having occurred after the study cut-off date and thus was not included in the study.

Fox and Collier (*7*) studied U.K. workers exposed to VC. In eight factories studied, they observed a total of four liver cancer deaths as compared to 1.64 expected. Three of these deaths occurred in factory 2, where only 0.13 would have been expected ($p < 0.01$). The authors stated that it was difficult to identify angiosarcoma of the liver from death certificates (the usual method of identification), since some of these deaths were classified as primary, some as secondary liver cancer, and others were not certified as cancer deaths at all.

The results from the Fox and Collier study probably represent an underestimate of the observed risk of death from cancer for the following reasons: (1) 75% of the study cohort was employed for less than ten years; (2) only 8% of the cohort was employed for more than 20 years; and (3) even

for those who completed 20 years of service, the authors stated that "because their service has only recently been completed, the follow-up period is too short to evaluate the carcinogenic effect of VCM." This statement obviously applies to the liver as well as to other sites.

Monson et al. (*8*) conducted a proportional mortality study of 161 deceased workers from two plants where VC was used. These plants were also studied by Waxweiler et al. (*5*). They observed eight deaths from liver and biliary tract cancer versus 0.7 expected; the risk ratio was 11.0.

Tabershaw and Gaffey reported the results of a cohort study of workers exposed to VC in 33 U.S. industrial facilities. The authors did not analyze the data separately for liver and biliary cancer. Thus, deaths for these causes are accounted for in the category of digestive organ cancer. As noted in Table 1, for the total cohort there were 19 deaths from digestive organ cancer and 21.7 expected. For the highest exposure cohort, with more than five years of exposure, there were 11 digestive organ cancer deaths observed versus 7.5 expected. None of the observations are statistically significant.

However, the risk of liver cancer in this cohort is submerged by including data for this cause of death in the analysis with digestive organ cancer deaths. Of the 19 digestive cancer deaths, the authors noted that seven were from liver cancer. Two of these liver cancer deaths were listed as angiosarcoma according to the diagnosis on the death certificate. An additional four deaths from liver angiosarcoma were identified in this cohort by the time the study was published in 1974. Two of these deaths had been categorized by death certificate diagnosis as primary liver cancer, and two had been certified under causes of death other than cancer, i.e., cirrhosis of the liver and hepatoma.

This study again demonstrates one of the inherent limitations of epidemiologic studies (incorrect diagnosis in relatively rare causes of death) that result in an underestimate of the relative cancer risk. An additional factor, indicated by the authors, that may have led to an underestimate of the risk in this study was that the group with no vital status determination, 15% of the population, began their exposure ten years before the group for whom followup was completed. As a result, some individuals with longer latency periods were omitted from the study. In addition, 57% of the cohort actually studied had less than 15 years of latency. Because of the healthy worker effect, the authors appropriately stated that SMRs higher than expected may be worthy of attention even if they are not statistically significant.

Buffler et al. (*10*) and Ott et al. (*11*) did not observe any liver cancer deaths among eight and twenty deaths, respectively, in their studies.

An unpublished study conducted by Equitable Environmental Health (*12*) reported the mortality of a cohort of workers from 37 U.S. industrial facilities. This study included data for the facilities studied by Tabershaw and Gaffey (*9*). Data were not analyzed separately for liver cancer. However, the category of death from cancer of the digestive organs, which includes liver cancer deaths, indicates a deficit of mortality. As shown in Table 1, even for those individuals who had achieved 20 or more years of latency, the SMR was only 70. It is somewhat unusual to observe such a deficit of mortality among workers who had achieved such a long latency period.

Brain Cancer in Humans

Brain cancer also has been associated with exposure to VC. A summary of the results of mortality studies is shown in Table 2. Although the number of cases upon which observations were based are small, Waxweiler et al. (*5*) and Byren et al. (*6*) demonstrated significant excesses of brain cancer. The relative risks were five and six, respectively. Waxweiler et al. (*5*) also noted an unusual distribution in the cell type of brain cancer. Of 10 brain cancer deaths identified among the VC-exposed workers, nine (90%) had a histologic diagnosis of glioblastoma multiforme. The tenth case had no confirmation of cell type. The authors contrasted this high proportion with that of the Yale autopsy series in which 33% of primary intracranial neoplasms were glioblastoma multiforme.

Fox and Collier (*7*) observed two brain cancer deaths as compared to 3.7 expected for the entire cohort. For those cohort members categorized as having high exposure, one brain cancer death was observed versus 0.4 expected. Monson et al. (*8*) demonstrated a fourfold risk of brain cancer.

Tabershaw and Gaffey (*9*) categorized brain cancer with "other and unspecified causes of cancer death;" therefore, it is not possible to determine the actual brain cancer risk identified in this study. Since the Tabershaw and Gaffey study (*9*) was a subset of the EEH study (*12*), the latter study was used to estimate the expected number of brain cancer deaths in the former study under the assumption that the age distributions were similar. The proportion of expected brain cancer deaths from "other and unspecified cancer deaths" in the EEH study (*12*) was then applied to the expected from this same category in the Tabershaw and

Table 2. Epidemiologic study results of VC-exposed workers as related to central nervous system.

Investigation	Site	Deaths		
		Observed	Expected	SMR
Waxweiler et al. (*5*)	Brain and CNS			
Total cohort		3	0.9	329
Latency > 15 yr		3	0.6	498[a]
Byren et al. (*6*)	Brain			
Total cohort		2	0.3	612[a]
Fox and Collier (*7*)	Brain			
Total cohort		2	3.7	55
Highest exposure		1	0.4	278
Monson et al. (*8*)	Brain			
Total deaths		5	1.2	4.2[a,b]
Tabershaw and Gaffey (*9*)	Other and unspecified			
Total cohort		17	11.8	155
Highest exposure, > 5 yr employment		7	3.5	204
All exposure levels	Brain	6	2.4[c]	250[a]
Buffler et al. (*10*)[d]				
Ott et al. (*11*)	All sites other than			
Total cohort	digestive and respiratory	6	6.8	88
Total cohort	Brain	2	0.7[c]	286
EEH (*12*)	Brain and CNS			
Total cohort		12	5.9	203[a]

[a] $p < 0.05$.
[b] Proportional mortality study risk ratio.
[c] Estimated.
[d] No brain cancer identified among 8 cancer deaths.

Gaffey study (*9*). As a result, 2.4 brain cancer deaths were estimated to have been expected and compared to six observed in the study. This difference is significant.

Buffler et al. (*10*) did not identify any deaths from brain cancer in their small cohort. Ott et al. (*11*) did not analyze their data separately for brain cancer, but rather included brain cancer deaths with cancer deaths from "all sites other than digestive and respiratory." Therefore, using an analytical technique similar to that described above, the proportion of expected brain cancer deaths among "all sites other than digestive and respiratory" from the EEH study (*12*) was applied to the expected in the study by Ott et al. (*11*). As shown in Table 2, there was a resultant estimated 0.7 brain cancer deaths expected as compared to two observed. The excess risk is estimated to be about threefold. The EEH study (*12*) also demonstrates a significant excess brain cancer among workers occupationally exposed to VC. In summary, the data for brain cancer appear to be more consistent between studies than the data for liver cancer, although the magnitude of the excessive risk is not as great for brain cancer.

Lung Cancer in Humans

As shown in Table 3, Waxweiler et al. (*5*) observed 11 lung cancer deaths as compared to 5.7 expected ($p < 0.005$) for cohort members who had achieved 15 or more years of latency. The authors also noted what appeared to be an unusual distribution in the histologic types of lung cancer. Of eight histologically confirmed lung cancer cases, five were classified as large cell undifferentiated, and three were categorized as adenocarcinoma. These cell types are different from those usually associated with a cigarette smoking etiology, i.e., small cell undifferentiated and epidermoid carcinomas.

With the exception of the study by Fox and Collier (*7*), the remaining studies show excess risks of lung cancer ranging from 7 to 200%. However, the reservation expressed by Fox and Collier (*7*), as mentioned earlier, about the short period of followup limits the interpretation of their study. This concern is supported by the observation that the SMR for total mortality was only 75, 75% of what would be expected on the basis of comparison to the standard population.

Table 3. Epidemiologic study results of VC-exposed workers as related to respiratory system cancer deaths.

Investigation	Site	Deaths		
		Observed	Expected	SMR
Waxweiler et al. (*5*)	Respiratory			
Total cohort		12	7.7	156
Latency > 15 yr		11	5.7	194[a]
Byren et al. (*6*)	Lung			
Total cohort		3	1.8	168
Fox and Collier (*7*)	Lung			
Total cohort		46	51.2	90
Highest exposure		2	3.7	54
Monson et al. (*8*)	Lung			
Total deaths		13	7.9	1.6[b]
Tabershaw and Gaffey (*9*)	Respiratory			
Total cohort		25	23.9	112
Highest exposure, > 5 yr employment		12	8.5	144
Buffler et al. (*10*)[d]	Lung			
Total cohort		5	1.7	289[a]
Long exposure duration		4	1.05	381[a]
Short exposure duration		0	0.45	—
Ott et al. (*11*)	Respiratory			
Total cohort		7	5.8	121
EEH (*12*)	Respiratory			
Total cohort		45	44.3	107
Highest exposure		7	5.1	141
Medium exposure		19	17.0	116
Low exposure		19	22.2	92

[a]$p < 0.05$.
[b]Proportional mortality study risk ratio.

Table 4. Epidemiologic study results of VC-exposed workers as related to lymphatic and hematopoietic system cancer deaths.

Investigation	Site[a]	Deaths		
		Observed	Expected	SMR
Waxweiler et al. (*5*)	(200–205)	4	2.50	159
Latency > 15 yr	(200–205)	3	1.70	176
Fox and Collier (*7*)	(200–207)	9	9.01	100
Monson (*8*)	(200–205)	5	3.4	1.5[a]
Tabershaw & Gaffey (*9*)	(200–203, 205)	6	6.06	106
Highest exposure, > 5 years employment		4	1.84	222
EEH (*12*)	(200–203, 205)	11	10.36	112
Latency > 20 years		4	3.10	136

[a]International Classification of Diseases, 7th Revision.
[b]*International Classification of Diseases, 8th Revision.*
[c]Proportional mortality study risk ratio.

As shown in Table 3, data from the EEH (*12*) and Buffler et al. (*10*) studies suggested a qualitative dose-response relationship between VC exposure and lung cancer risk. However, retrospective categorization of high, medium and low exposure, as was used in the EEH study (*12*), must be viewed with caution because of the subjective nature of judgment. The study by Buffler et al. (*10*) is particularly noteworthy; within a small cohort of only 464 workers, a fourfold risk of lung cancer was observed. When the investigators examined the effect of smoking, under the extreme assumption that those with unknown smoking habits were smokers, the data still demonstrated a significant

excess of lung cancer (5 observed versus 1.98 expected.)

Cancer of the Lymphatic and Hematopoietic System in Humans

Table 4 summarizes data on cancer of the lymphatic and hematopoietic systems among workers exposed to VC. The relative risks for various studies ranged from 1.0 to 2.2, and none of the results demonstrated a significant excess. Although somewhat suggestive, the data need to be further analyzed by latency period and exposure levels combined. Analysis of data separately for lymphatic cancers and leukemia might also lead to meaningful observations.

Summary

In summary, epidemiologic evidence demonstrates that the carcinogenic effects of VC in humans extend beyond the liver. The brain and lung should also be considered target organs. Some studies indicate that the lymphatic and hematopoietic systems are also involved. These observations in humans are supported by studies demonstrating the induction of cancer of these same sites in experimental animals.

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